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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Scott Arouh and Cornelius Diamond) Confirmation No. 4817

Serial No.: 09/611,220) Group Art Unit: 1631

Filed: July 6, 2000) Examiner: Allen. M.

For: **NEURAL-NETWORK-BASED IDENTIFICATION, AND APPLICATION, OF GENOMIC INFORMATION PRACTICALLY RELEVANT TO DIVERSE BIOLOGICAL AND SOCIOLOGICAL PROBLEMS, INCLUDING DRUG DOSAGE ESTIMATION**

Atty's Docket No.: DIA 0002P

San Diego, California
March 19, 2003

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Transmitted herewith is/are the following document(s) related to the above-identified patent application:

( )	Acknowledgement of Receipt Card	( )	Request for Reconsideration
( )	Disclosure Statement/37 CFR §1.56	( )	Affidavit Under 37 CFR §1.131
( )	Preliminary Amendment	( )	Affidavit Under 37 CFR §1.132
(X)	1 Month Extension of Time Under 37 CFR §1.136 (fee noted below)	( )	Notice of Appeal
		( )	Appeal Brief (in triplicate)
( )	Response Under 37 CFR §1.111	( )	Reply Brief
( )	Amendment Under 37 CFR §1.115	( )	Certificate of Mailing
(X)	Amendment After Final Rejection Under 37 CFR §1.116	( )	Communication
		( )	Change of Address in Application
( )	Power of Attorney by Inventor		

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CLAIMS AS AMENDED

	Claims Remaining After Amendment		Highest No. Previously Paid For		Present Extra		Rate		Add'l Fee
Total Claims:	3	minus:	34	:	0	x	$ 9	=:	$
Ind. Claims :	1	minus:	12	:	0	x	$42	=:	$
Multiple Dependent Claim Fee								:	$
Fee for Extension of Time (1 Months)								:	$ 55
							TOTAL FEE DUE	:	$ 55

(X) Applicant(s) hereby petition for a 1 month extension of time under 37 CFR §1.136 (fee noted above).
( ) No additional fee is required.
(X) Enclosed is a check for $ 55 in full payment of the above fees. The Commissioner is hereby authorized to charge payment of any additional patent application filing fees under 37 C.F.R. §1.16, 37 C.F.R. §1.17, or patent issue fee under 37 C.F.R. §1.18 associated with this communication or credit any overpayment to Deposit Account No. __-____.

A duplicate copy of this letter is enclosed.

Sincerely yours,

William C. Fuess

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[X] Attorney of Record
[ ] Filed Under 37 CFR §1.34(a)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date written below.

March 19, 2003	William C. Fuess	William C. Fuess
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8 Amdt TG

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Atty's Docket No.: DIA 0002P

San Diego, California
March 19, 2003

AMENDMENT UNDER 37 C.F.R. §116

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

DO NOT ENTER MPK 3/31/03

In response to the second and final Office Action mailed November 19, 2002, the time for response to which being extended by the accompanying Petition, please enter and consider the present amendment under Rule 116.

In The Claims

Please cancel claim 8, removed from consideration, without prejudice.

REMARKS

Claims 10 and 14-15 are in the application. Entrance of the present Amendment under Rule 116, and reconsideration, are respectfully requested.

1. Requirement for Restriction Under 35 U.S.C. §121

Per the second sheet of the previous Office Action mailed

October 1, 2001, claim 9 -- as well as claims 10 and 14-15 -- was listed as under consideration.

Claim 9, now in the present Office Action apparently restricted from consideration, is now canceled without prejudice.

2. Information Disclosure Statement

Applicants do not know of any art preceding the date of their claimed invention which is more relevant to patentability than that art already made of reference, and correspondingly do not submit an Information Disclosure Statement.

It is to be recalled that an Information Disclosure Statement is primarily to make of record art relevant to the patentability of the invention, and not generally to broadly educate in the state of the art to which the invention pertains at the time the patent application was filed.

3. Missing Pages

Applicant believes what is before the Examiner at pages 61-62 **is** that change page that was submitted during Applicants' previous Amendment response of August 23, 2002.

In the first place, any defect with the pages 61-62 in the application as filed was an artifact of printing, undetected by Applicants at time filing, where a page advance, **and nothing else**, occurred.

The Examiner feels that there is text missing from page 61-62.

There is **no** text missing. Perhaps this is unclear to the Examiner since there is a parenthetical remark in the text. Consier the contiguous text of the complete paragraph that breaks at pages 61-62:

> 6.5 Use for Choosing Optimal Drugs for a Given Patient
> The above comparison of drug efficacies allows the development of an automated technique for choosing optimal drugs for a given patient. A given patient's genome is first

scanned and the problematic genomic inputs (such as problematic alleles) identified (as those elements of the genomic inputs that are also present in the universal functional categories). A software program then identifies which drug is expected to perform the best on the patient's set of problematic inputs. The program does this by comparing the effectiveness of different drugs on the problematic inputs found in the given patient.

If the above paragraph is regarded without the parenthetical remarks it becomes:

6.5 Use for Choosing Optimal Drugs for a Given Patient
The above comparison of drug efficacies allows the development of an automated technique for choosing optimal drugs for a given patient. A given patient's genome is first scanned and the problematic genomic inputs identified. A software program then identifies which drug is expected to perform the best on the patient's set of problematic inputs. The program does this by comparing the effectiveness of different drugs on the problematic inputs found in the given patient.

It may be understood that the meaning of the sentence "split" between pages 61 and 62 is clear, i.e. the subject and verb are in agreement, and the context of the sentence fits within the thrust of the paragraph. Merely adding parenthetical remarks does not change this. The fact that the period is after the parenthetical remarks makes the sentence grammatically correct.

Accordingly, there is an unwarranted page break, extending across a single sentence of text, but **no** material is missing. A replacement page has been submitted in the Applicants' previous Amendment mailed August 23, 2002. No substantive new material is added. Entry is requested.

3. Rejections Under 35 U.S.C. §112, First Paragraph

Claim 10 was rejected under 35 U.S.C. §112, first paragraph.

The Examiner requires identification of support in the specification for the amended language in the (i) preamble and (ii) body of claim 10.

The Examiner apparently **continues** to believe "that the

information required to practice the [claimed method of the] invention is not available, and does not exist" (Office Action of April 23, 2001 (i.e., **not** the present Office Action, but the one previous thereto) at page 3, lines 8-9).

In Applicants' Amendment response of August 23, 2003, Applicants told the Examiner: "In fact, (i) such information does exist, and (ii) is well known to practitioners of the art to which the invention pertains. Further, (iii) equivalent information regarding "genomic data including alleles and/or characteristic SNP patterns" to that which is suitable for use in the present invention **has** before the filing date of Applicants application been used to realize "Pharmogenetic prediction of clozapine response" [citing an paper previously supplied the Examiner].... Still furthermore, (iv) using publicly available data regarding "genomic data including alleles and/or characteristic SNP patterns", Applicants have reduced their own invention to operative practice."

The Examiner rejects showings (i)-(iv), discussing the same, and **continues** her rejection of claims 10 and 14-15 under 35 U.S.C. §112, first paragraph.

The rejection is respectfully traversed.

In response Applicants submit the attached AFFIDAVIT UNDER 37 C.F.R. §1.132 of Dr. Nicolas Schork, University of California, San Diego (having such qualifications as are set forth in paragraph 1. of the AFFIDAVIT). This AFFIDAVIT should suffice to explain to the Examiner why her views as to the supposed unavailability (at the July 6, 2000, time of application filing) of genomic data upon which Applicants' claimed method operates are flawed. In fact, (i) this information did and does exist, and (ii) is well known to practitioners of the art to which the invention pertains.

The AFFIDAVIT would perhaps best be first read in its entirety. If found illuminating, and persuasive, it will perhaps

not be necessary for the Examiner to reach the next following legal argument, quoting where appropriate from the AFFIDAVIT, of sections 3.1.

Finally, and if the Examiner still maintains her objection, some comments of a general sort, not necessarily couched in the language of the Patent Law and rules but hopefully persuasively appealing to reason, are contained in sections 3.2

3.1 The Legal Basis For Making/Maintaining/Sustaining any Rejection Under 35 U.S.C. §112, First Paragraph

In the following subsections Applicants discuss the legal basis for making/maintaining/sustaining any rejection Under 35 U.S.C. §112, first paragraph, with reference where appropriate to the enclosed AFFIDAVIT UNDER 37 C.F.R. §1.132 of Dr. Nicolas Schork, and/or materials already submitted, and of record.

3.1.1 The Test of Enablement

Applicants start by restating, for the record, the statutory basis of any enablement analysis.

"Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. T he standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require

that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Determining enablement is a question of law based on underlying factual findings. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).....

"The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)." (MPEP §2164.01 Test of Enablement.)

Applicants argue that there is **no** substantial experimentation, let alone any "undue experimentation", necessary

to create the databases linking genomic information and drug response upon which Applicants' inventive method operates.

3.1.2 Standard Modes of Administration are Subsumed in Any Statement(s) as to How to Use a Claimed Invention

"If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. In re Johnson, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); In re Hitchings, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also In re Brana, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993)." (MPEP: 2164.01(c) How to Use the Claimed Invention)

Dr. Schork presents facts that "(1) patient genomic information sufficient to practice the invention, to wit: to train and to exercise the neural network, **was** available on 07/06/00, **and**, to the extent that the Examiner or any finder of fact should refute this my assertion, (2) this data might alternatively readily be obtained as of 07/06/00 by a practitioner of the genomic arts having but such routine skills as then existed, and without undue, and, indeed, with little or even **no**, experimentation". (Schork AFFIDAVIT paragraph 7.) These modes of (i) accessing, and/or (ii) obtaining genomic data were all **standard**, known and contemplated as of the time of application filing!

3.1.3 The Specification Must Be Enabling to Persons Skilled in the Art

"The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. Where different arts are involved in the invention, the specification is enabling if it enables persons skilled in each

art to carry out the aspect of the invention applicable to their specialty. In re Naquin, 398 F.2d 863, 866, 158 USPQ 317, 319 (CCPA 1968).

"When an invention, in its different aspects, involves distinct arts, the specification is enabling if it enables those skilled in each art, to carry out the aspect proper to their specialty. "If two distinct technologies are relevant to an invention, then the disclosure will be adequate if a person of ordinary skill in each of the two technologies could practice the invention from the disclosures." Technicon Instruments Corp. v. Alpkem Corp., 664 F. Supp. 1558, 1578, 2 USPQ2d 1729, 1742 (D. Ore. 1986), aff'd in part, vacated in part, rev'd in part, 837 F. 2d 1097 (Fed. Cir. 1987) (unpublished opinion), appeal after remand, 866 F. 2d 417, 9 USPQ 2d 1540 (Fed. Cir. 1989). In Ex parte Zechnall, 194 USPQ 461 (Bd. App. 1973), the Board stated "appellants' disclosure must be held sufficient if it would enable a person skilled in the electronic computer art, in cooperation with a person skilled in the fuel injection art, to make and use appellants' invention." 194 USPQ at 461." (MPEP: 2164.05(b) Specification Must Be Enabling to Persons Skilled in the Art)

Clearly Applicants' invention involves the arts of computer programming, and, the Examiner would maintain, the gathering of genomic data. In fact, it is the later that is **easier**. As explained by Dr. Schork: "The articles I now cite are prominent, their teachings clear and obvious, and any practitioner in the genomic data arts would have no problem in recognizing applicability of **both** (i) genomic data **already gathered (!!)**, and (ii) standard clinical methods of so gathering genomic data, to the claimed method of Applicants' invention. (Schork AFFIDAVIT paragraph 12.) (emphasis in original)

3.1.4 Experimentation is Permissible; and the Quantity Thereof is Only One Factor in Determination of "Undue Experimentation"

The Examiner seems to find that both (i) the quantity, and (ii) the cost, to gather such genomic data as she finds useful to the exercise of Applicants' claimed invention would be great. This is **not** the sole test.

The genomic data, and the expression of this data in relation to drug dosage results, is straightforwardly gathered. Insofar as the quantity of this information is desirably great, and the cost of gathering the same commensurately great, then so also are the value of the results obtained by Applicants' inventions very great, as explained in Applicants' specification. Remember, Applicants inventions can not only identify genetic relationships that make administration of certain drugs unavailing and wasteful, but can identify relationships that make administration of certain drugs positively harmful and dangerous to certain patients (but not to others)!

"The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " **'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'** " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). **Time and expense are merely factors in this consideration and are not the controlling factors.** United States

v. Telectronics Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989)....

"... Time and difficulty of experiments are not determinative if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

"I. EXAMPLE OF REASONABLE EXPERIMENTATION

In United States v. Telectronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989), the court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation."

(MPEP: 2164.06 Quantity of Experimentation) (boldface added)

3.1.5 <u>The Burden Is on the Examiner to Establish a Reasonable Basis to Assert that the Enablement Requirement Has Not Been Met</u>

"Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. For terms that are not well-known in the art, or for terms that could have more than one meaning, it is necessary that the examiner select the definition that he/she intends to use when examining the application, based on his/her understanding of what applicant intends it to mean, and explicitly set forth the meaning of the term and the scope of the claim when writing an Office action. See Genentech v. Wellcome Foundation, 29 F.3d 1555, 1563-64, 31

USPQ2d 1161, 1167-68 (Fed. Cir. 1994).

"In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

"According to In re Bowen, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments. See also In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citing In re Bundy, 642

F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981)) (discussed in MPEP ° 2164.07 regarding the relationship of the enablement requirement to the utility requirement of 35 U.S.C. 101).

"While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP §2164.01(a)(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP §2164.06(a)(a). References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

"In accordance with the principles of compact prosecution, if an enablement rejection is appropriate, the first Office action on the merits should present the best case with all the relevant reasons, issues, and evidence so that all such rejections can be withdrawn if applicant provides appropriate convincing arguments and/or evidence in rebuttal. Providing the best case in the first Office action will also allow the second

Office action to be made final should applicant fail to provide appropriate convincing arguments and/or evidence...." (MPEP: 2164.04 Burden on the Examiner Under the Enablement Requirement)

The Examiner has made the basis for her objections to Applicants' alleged non-enablement clear enough: the problem is that she has maintained them in the face of evidence already introduced.

The Examiners' finding that Applicants' showing of suitable data was in possession (at a time before filing) of both Genaissance and Pharsight is **un**convincing is respectfully traversed. If multiple parties in possession of what the Examiner would allege are **independent, and un-shared** databases appropriate to Applicants' invention is not evidence that such databases **can** be routinely constructed, what is?

3.1.6 Any Determination of Enablement Must be Based on Evidence as a Whole.

"Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. In re Brandstadter, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art.

"Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. In re Buchner, 929 F.2d 660, 661, 18

USPQ2d 1331, 1332 (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); cf. In re Alton, 76 F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) (declarations relating to the written description requirement should have been considered)....

To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works.... (MPEP §2164.05 Determination of Enablement Based on Evidence as a Whole).

Clearly Applicant now provides, in the form of materials previously submitted, and the Schork AFFIDAVIT, the required evidence. The Examiner has also misunderstood Applicants' evidence of the reduction of their invention to operative practice under contract with NIH. Although this reduction does **not** conclusively mean that no further innovation, and/or undue experimentation, occurred in the time since July 6, 2000, in actual fact no such innovation and/or undue experimentation occurred, and Applicants' **successful** reduction to operative practice was in full accordance with their own specification!

"The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion. The determination should always be based on the weight of all the evidence. (MPEP: 2164.05 Determination of Enablement Based on Evidence as a Whole)

Applicants submit that the explanatory Schork AFFIDAVIT is

very weighty evidence indeed.

3.1.7 Relationship of Predictability of the Art and the Enablement Requirement

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.

"The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art...." (MPEP §2164.03 Relationship of Predictability of the Art and the Enablement Requirement)

In the case of the "genomic data including alleles and/or characteristic SNP patterns" (claim 10) that the Examiner finds so mysterious and unavailable to / unrealizable by (at least without undue experimentation) a practitioner of the genomic data

acquisition arts, the Schork AFFIDAVIT makes clear:

> "It has been well-known that although there are many genes that influence the pharmacokinetic properties of individual drugs, there is a family of ~30 genes known as the cytochrome P450 (CYP450) gene family, characterized in 1982 (see, e.g., Gotor and Fujii-Kuriyama(1989)....
>
> "It is well known that there is a great deal of variation in CYP450 genes (see. e.g., Weber 1997, op cit.)....
>
> "The differences among individuals that result from this genetic variation can, and are known to, influence the function of CYP450 genes (see, e.g., Weber 1997, op cit.).
>
> "Since this family of genes is known to influence drug metabolism, and there are known to be variations in the genes in this family that influence metabolism of endogenous compounds, variation in these genes are likely to (and have been documented to) influence the amount of drug required to elicit a particular effect in different individuals....
>
> "Ultimately, if a practitioner did not know *a priori* which, e.g., CYP450 genes were involved in the metabolism of a particular drug, and further, which genetic variations in CYP450 genes influenced variation in drug metabolism (which is often the case), he or she could 'genotype' a number of individuals (i.e., assess which variant at a site in a gene individuals possess) who have been or are being treated with a particular drug who have also been administered different doses based on efficacy of the drug (a routine practice by physicians and clinicians), and then use algorithms like those taught in the patent application to determine which genetic variants influence dose effects among the individuals studied."

Schork AFFIDAVIT paragraphs 23-27. Simply put, Applicants claimed method will work on a genomic database that was **preexisting** at the time of application filing.

The Examiner may wonder about access to data. To publish in a journal the source data from which the investigative findings and/or conclusions are derived **must** be made available, on request, to anyone who wants it. The Schork AFFIDAVIT says:

> "This emphasis led to the creation of databases (see, e.g., Collins FS, Brooks LD, Chakravarti A (1998). A DNA polymorphism discovery resource for research on human genetic variation. Genome Research. 8:1229-31; Gu et al. 1998, op cit.; and Wang et al. 1998, op cit.) containing information about variation in human genes."

Schork AFFIDAVIT paragraph 43.

The art of the creation of genomic databases is predictable, and even routine.

3.1.8 Undue Experimentation Factors

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

"In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). In Wands, the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. In re Wands, 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related

to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407." (MPEP §2164.01(a) Undue Experimentation Factors)

The level of skill in the art to which Applicants' invention pertains is high. All of the genomic data gathering methods -- **including simple library research, followed by requests to investigators for their public domain source data** -- needed to practice Applicants' invention are well known.

"It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407.

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

"The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. These factual considerations are discussed more fully in MPEP §2164.08 (scope or breadth of the claims), §2164.05(a) (nature of the invention and state of the prior art), §2164.05(b) (level of one of ordinary skill), §2164.03 (level of predictability in the art and amount of direction provided by the inventor), §2164.02 (the existence of working examples) and §2164.06 (quantity of

experimentation needed to make or use the invention based on the content of the disclosure)." (MPEP 2164.01(a) Undue Experimentation Factors)

As stated in the Schork AFFIDAVIT:

> "This emphasis [on identifying genetic variations] led to the creation of databases (see, e.g., Collins FS, Brooks LD, Chakravarti A (1998). A DNA polymorphism discovery resource for research on human genetic variation. Genome Research. 8:1229-31; Gu et al. 1998, op cit.; and Wang et al. 1998, op cit.) containing information about variation in human genes.
>
> "These databases are, and have been for years, publicly accessible such that any practitioner could query them."

(Schork AFFIDAVIT paragraphs 43 and 44).

See also:

> "If variations in the genes are found, then individuals who have been prescribed relevant drugs can be genotyped in an appropriate way (see, e.g., Ross P, Hall L, Smirnov I, Haff (1998). High level multiplex genotyping by MALDI-TOF mass spectrometry. Nature Biotechnology 16:1347-51.) and association studies can be pursued...."

(Schork AFFIDAVIT paragraph 32).

In simplest terms, it is well known how to genotype humans. Genotyping of humans who take drugs ("drug results" in claim 10) straightforwardly produces the databases upon which Applicant's invention operates.

3.2 General Discussion

Applicants have submitted evidence in the form of an AFFIDAVIT.

Applicants have argued in section 3.1 above the application of the law to this evidence.

However, the very fact that Applicants' application,

constructed with great care specifically **to be enabling** has been found wanting under 35 U.S.C. §112, first paragraph, perhaps deserves a bit of discussion, even if not rigorously linked to 35 U.S.C. §112, first paragraph, and/or the patent examination process, as to what patent disclosure, and patenting, is, in Applicants' opinion, all about.

The Examiner comments adversely on amendments to the claims; rejecting claims 10 and 14-15 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. This is a new matter rejection.

Applicants traverse this rejection. The amendment to the claims is entirely consistent with the instant invention, which continually stresses the need for a therapeutical dosage. Please read the first three sections of the original patent application. Secondly, the original patent application and the one that it references talk about optimizing training by genetic algorithms so this is a valid modification to help clarify the teaching process. Thirdly, the reduction in computational complexity of said algorithm is clearly taught in the body of the patent in section four.

The Examiner comments adversely on the enablement of the claimed invention. Claims 10 and 14-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, for reasons of record, etcetera.

The application specification must teach someone "who is skilled in the art" how to make something or perform some action. This is regardless if the item that the patent refers to has actually been built. This is why the people who conceive the

idea get credit for the invention, and not the ones who build it or perform the methodology according to directions. If the raw materials are not available until the future this does not matter. Enablement comes into the equation only if something as not been sufficiently EXPLAINED such that the methodology or mechanism fails to work, which is NOT the case here.

Applicants disclosure **is** enabling because it explains fully how to carry out Applicants's claimed invention: CONSTRUCTING a PREDICTOR of ADVERSE EVENTS, DRUG EFFICACY AND/OR DRUG DOSAGE from previously assembled genetic data sets. If one invents a better mousetrap one does not need a mouse to get a patent on the idea.

The 'raw material' of Applicants' invention is (1) human genetic information, along with (ii) physiological data which has been around ever since humans have been around. To get relevant DNA from a person, one does not need blood. Indeed, we are continuously shedding DNA through hair loss, skin flaking, saliva, etc. To get somebody's DNA is not very hard. For this specific claim, if Applicants operating as a company wanted to get DNA then they would just follow around people with a certain drug side effect and vacuum up the dermis that their body gives off. Medical chart data could be gotten in an interview. True, to extract the DNA would take a little bit of lab work, but the techniques involved have been automated since the late 1980's and the level of knowledge required would be a high school education.

So why do neither Applicants, nor any other clear-thinking investigators do this? Because of the time and expensed involved would divert Applicants, and their company's, efforts away from what is of real value (and what takes considerable skill) namely, UTILIZING data generated once one genotypes the information.

This is what Applicants' patent application is all about. Money to realize one's idea -- at least in fullest expression and force -- should **not** be a barrier to granting a patent? If it

were, quite a few patents would be invalidated, including the blocking patents, which have become so popular these days. Remember, the Apollo moon landing scenario was patented many years before it was realized. How much did it cost to implement that invention?

While biobanks that contained patient information sprang up in the late 1990's, there have been several sample repositories (i.e. blood sample and patient information) through the National Institutes of Health and private institutes such as the HUGO working group. See (http://ariel.its.unimelb.edu.au/~cotton/discuss.htm). These biobanks that have been around before the present application was filed.

To obtain appropriate biogenetic information, one usually goes through a peer-review process, so your average guy off the street probably would be rejected but "a person skilled in the art" would be someone who is a researcher in the field, i.e. somebody who could execute the claim that is taught in Applicants' patent.

Finally, at the time of the application filing, there were numerous private researchers at universities or institutes who maintained the necessary information to execute the patent described here, and the only barrier is money. One such example is John Kelsoe, professor of medicine at the University of California, San Diego, who has maintained a blood sample databank with associated patient information on lithium in bipolar patients (with the adverse effect of the drug being obesity) since 1989.

Again, Applicants submit that all this information existed (and exists) in data repositories, and one just had to find it, which is just legwork and convincing the Institutional Review Board that your application (in this case a predictor of side effects based on genetic and physiological data) is worthwhile

effort to be associated with. This a person "a person skilled in the art" could do. Moreover, access is time-independent, i.e. peer-reviewed studies in medicine have been going on since the 1600's (i.e. getting access to cadavers) so getting the information required for practice of Applicants' invention could readily be done at the time of the application submittal.

If the patent Examiner still objects in the face of all this evidence and argument, let us examine specific examples that will remove once and for all any doubt that there was the information required for enablement of Applicants' claimed invention. Please note that if the Examiner chooses to refute these examples, then the Examiner may have to allege her superior domain knowledge or relevant skill level and/or the state of the art at the time of the submittal of Applicants' application.

First, let us look at the information submitted previously. The 'Hypertension Response Prediction' NSF Final report was submitted well after the application filing. It was submitted to show that patient genotype-phenotype patient information was available. Applicants' company Prediction Sciences, Inc. licensed this specific information from Pharsight, Inc. in January of 2001. However, Pharsight in turn licensed the data from Duke University over the course of 1999, which shows data was available at the time of the patent application, if an individual or organization had the financial wherewithal to obtain it.

The Examiner states "Page 30 documents that the biggest hurdle was obtaining the patient data source and that cost prevented the inventors for {from} generating a patient pool designed for the study." With all due respect, this is ABSOLUTELY NOT what page 30 says at all. Page 30 states that while Applicants "were forced to sort through over 1200 patient charts by hand... to obtain the patients that met Applicants' protocol for inclusion in this study" it also states Applicants "

successfully surmounted this obstacle to bring this study to conclusion on-time".

This is just further evidence that such a task can be done. In fact, it **was** done by the Duke researchers who gathered the data pre-2000 for Pharsight, Inc. and Applicants just made it better FOR THEIR SPECIFIC PROTOCOL.

The Examiner further states that "the document concerns the instant invention and acknowledges on page 5 that a great deal of software and data preparation had to be invented in order to successfully execute the method". In this case the Examiner is making a false assumption based on lack of knowledge of software development. What is claimed and taught in the instant invention is a methodology for predicting adverse effects; on page 5 what was done was "-Pre-processing sorting and annotating SNP software created" This has to do with putting the raw data into a database program and has nothing to do with the instant invention;

"Advanced neural network routines developed on MATLAB environment" This has to do with implementing our algorithms that Prediction Sciences had ALREADY CREATED at the time of the instant invention on the MATLAB platform, which is a software development process called porting to a new platform (i.e. coding in a new computer language) and is not claimed anywhere in the instant invention;

"Neural network algorithms validated on NCI AML/ALL gene expression data" Here Applicants just used what they had already invented on a publicly available dataset (available since 1999: Golub et al. (1999). Molecular classification of cancer: class discovery and class prediction by gene expression monitoring, *Science*, Vol. 286:531-537);"Novel Bayesian thresholding technique invented" This is a pre-processing data technique nowhere referred to in the instant invention; And"Novel Functional Partitioning Method invented for future neural network design"

This is a neural network architecture nowhere referred to in the instant invention.

The Examiner further goes on to say that data from Pharsight and Genaissance would not be available to one skilled in the art. As to the former the Examiner has been proved wrong, as one could license the data from its source, Duke University; and as to the latter their information came from university studies, which are done by someone "with ordinary skill in the art".

The Examiner makes the further unsubstantiated claim that these studies would not have included all the information necessary for the method claimed. Unless the Examiner is prepared to show otherwise, the applicant states that patient studies have been done for decades and are designed by people trained to run them, i.e. those with "ordinary skill in the art". The information is drug(s) taken (maintained as a matter of record, obvious); drug dosages and/or efficacy data (in patient chart medical records which is part of any drug study) adverse event(s) (also in patient medical records); genomic data (gained as a tissue or blood sample and then genotyped by techniques that have been around for at least two decades at the time of this writing).

Applicants maintain that a person with ordinary skill in the art could have run a study to gain the necessary information for the instant invention. To back up this claim, Applicants have submitted the following affidavit from Dr. Nicholas Schork who clearly refutes the assertions of the Examiner.

The Examiner further asserts that Applicants "investigated a known pathway with known genomic markers and known drugs for treatment" and that "it would have been more difficult to determine such associations for uncharacterized pathways with no known genomic marks {markers} and known drugs for treatment". This statement is puzzling, as Applicants wonder if the Examiner is asserting that an invention has to completely elucidate the

mechanism behind the problem it solves? If this is the case, the Examiner might want to invalidate nearly all patents dealing with objects involved in a nonlinear mechanism, i.e. electrical, aeronautical, chemical power systems, etc. as the physics of these systems is still largely unknown today. In addition, the patent Examiner might want to invalidate all drug patents, as the mechanism of action is largely not proven in a large percentage of current drug therapies. If it were, the medicine would work the same in everybody, which took the drug, negating the need for the instant invention.

The incongruity of the previous statements suggest that the Examiner should take a closer look at what is being claimed in the instant invention, which is a methodology to build a predictor of adverse events, drug dosage, drug efficacy, and/or some clinical outcome of interest, NOT the solution to all biological problems and/or questions! As to the availability of markers, Applicants remind the Examiner that a 'working draft' of the human genome was completed on June 26, 2000 and therefore all SNP markers (patterns of which Applicants reference in the instant invention) of interest (i.e. in genomic coding regions) were technically known at this time.

The Examiner still further asserts that this is a complex problem, and that a person skilled in the art would have trouble implementing such. Applicants agree that this is a complex problem with many facets and is non-obvious; ergo, the reason why Applicants submitted the patent in the first place to teach those skilled in the art! If the Examiner has a problem with "the computational complexity of such a situation" Applicants suggest to the Examiner to those accompanying claims which the Examiner restricted as separate inventions in her first office action.

The Examiner states "Associations of alleles to responders or non-responders is {are} not analogous to the claimed method for predicting optimal drug dosage and/or drug efficacy for an

individual patient. As such, arguments with respect to Arranz et al is {are} not persuasive". Applicants agree that the method is different from the claimed method, which is the reason for the instant invention! Applicants remind the Examiner that Exhibit B of Applicants' predecessor amendment was given to refute the claim that "the information required to practice the [claimed method of the] invention is not available, and does not exist" from the first office action mailed April 23, 2002.

Furthermore, if the Examiner read the article it shows the investigator taking a candidate gene approach, taking previously UNKNOWN alleles and then correlating them with response in a linear fashion; our instant invention takes this much further by able to incorporate nonlinear associations as well.

As to the Examiner's assertion that the evidence provided does not have drug dosage data, Applicants wish to assure the Examiner that this is routine and since the study examined the phenotype of drug response, not dosage, this was not reported. Drug dosage is just one of the phenotypes that the instant invention claims as a methodology to build a predictor for.

As stated many times previously, the instant invention is a methodology for computationally building a predictor of a clinical outcome of interest, and this information is gathered routinely in most clinical studies. If the Examiner has any doubt of this she should read the many references pertaining to previous pharmacogenomic studies given in the original patent application, as well as any drug advertisement in a common magazine.

Finally, the Examiner states various examples around the time of the instant invention of the difficulty of mapping traits to disease. Applicants again agree with the Examiner of this fact, and suggest that if the researchers quoted read Applicants patent, then they would have been alleviated of their uncertainty. The methodology claimed by the Applicants is most

certainly NOT the haplotyping technique of Judson, et al. as this is just a technique of linear correlating clustered alleles on a single locus to disease phenotypes, with no regard to any nonlinear correlations that would reduce the number of alleles under study among other problems. The fact that the authors require massive amounts of haplotypes just further shows the need for the instant invention.

The Examiner concludes by rejecting claims 10 and 14-15 under U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". Applicants are particularly puzzled at this statement as it is clear from the text of the claim " A method of predicting a therapeutically optimal drug dosage and/or drug efficacy for a particular individual patient in respect of genomic data…the method comprising training a neural network on numerous examples of genomic data…" what is being produced, i.e. a methodology for computationally predicting an outcome of clinical interest. This methodology is to apply to all disease, and the (presumed) assertion by the Examiner that the particular disease has to be pointed out is irrelevant. This is like saying the patent on the light bulb that Edison invented was invalid if it did not tell the particular room it is good for illuminating, or the transistor patent is invalid because it did not tell the device it would be used for.

4. Summary

The present remarks have discussed and overcome each of the bases for the rejections presented in the Office Action. No new subject matter has been introduced by the present amendment.

In consideration of the preceding remarks, the present amendment under rule 116 is deemed worthy of entrance, and the present application is deemed in condition for allowance. The

timely action of the Examiner to that end is earnestly solicited.

Applicant's undersigned attorney is at the Examiner's disposal should the Examiner wish to discuss any matter which might expedite prosecution of this case.

Sincerely yours,

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[ ] Filed Under 37 CFR §1.34(a)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date written below.

March 19, 2003	William C. Fuess	
Date	Typed Name of Person Mailing Correspondence	Signature of Person Mailing Correspondence

AFFIDAVIT UNDER 37 CFR 1.132

1. I, Nicholas Schork, Ph.D., am currently a Professor of Psychiatry at the University of California at San Diego; previous to my appointment at UCSD I was an Associate Professor of Epidemiology and Biostatistics at Case Western Reserve University in Cleveland, Ohio and an Associate Professor of Biostatistics at Harvard University; formerly also the Associate Director of the Program for Population Genetics at the Harvard School of Public Health, as well as an Adjunct Associate Staff Scientist at the Jackson Laboratory in Bar Harbor, Maine; between 1999-2000 I was on leave of absence 1999-2000 to conduct research as the Vice President of Statistical Genomics at the French Biotechnology company, Genset, in order to help guide efforts to construct the first high-density map of the human genome.

2. I work on theoretical and applied aspects of the genetic basis of multifactorial traits and conditions, where I am (i) a member of a number of scientific journal editorial boards, (ii) a frequent participant in U.S. National Institutes of Health-related steering committees and review boards, and (iii) on the advisory board of five different companies.

3. I have published over 150 scientific articles and book chapters on the analysis of complex, multifactorial traits and diseases.

4. I have a B.A. in Philosophy, an M.A. in Philosophy, an M.A. in Statistics, and a Ph.D. in Epidemiology all from the University of Michigan in Ann Arbor, Michigan.

5. I have been supplied with, and have read,

(i) U.S. Patent application serial number 09/611,220, for NEURAL-NETWORK-BASED IDENTIFICATION, AND APPLICATION, OF GENOMIC INFORMATION PRACTICALLY RELEVANT TO DIVERSE BIOLOGICAL AND SOCIOLOGICAL PROBLEMS, INCLUDING DRUG DOSAGE ESTIMATION as filed on 07/06/00 ["the Application"].

(ii) the First PTO Office Action mailed 10/01/01 to the Application;

(iii) Applicants' (first) AMENDMENT UNDER 37 C.F.R. §1.115 mailed 11/01/01;

(iii) the Second PTO Office Action mailed 04/23/02 to the Application, and the reference art cited therein;

(iv) Applicants' (second) AMENDMENT UNDER 37 C.F.R. §1.115 mailed 08/23/02, and the attached EXHIBITs;

(v) the Third, and Final, PTO Office Action mailed 11/19/02 to the Application; and

(vi) a copy of 35 U.S.C. §112, including its first paragraph;

(vii) a copy of MPEP chapter 20, including sections MPEP 2164.01(c)-MPEP 2164.01.

6. From the materials of 5. above, and especially (v) the Third, and Final, PTO Office Action mailed 11/19/02 to the Application, I understand the issue to be in general whether or not the

application as filed on 07/06/00 did contain within its specification subject matter sufficient to permit a routineer in the art to which the invention pertains to successfully practice as of 07/06/00 the invention, as such invention is presently claimed in the pending claims of (iv) Applicants' (second) AMENDMENT UNDER 37 C.F.R. §1.115 mailed 08/23/02, without undue experimentation; and the issue to be in particular whether, as of 07/06/00, a practitioner with ordinary skill in the art to which the invention pertains would either (1) have had available patient genomic information sufficient to practice the invention, to wit: to train and to exercise the neural network, or, if not then available, (2) would have been able to derive such information without undue experimentation.

7. Without stating legal conclusions -- which I understand as discussed in section 10. below that I am not to do -- in this AFFIDAVIT, I say in advance that I will present facts that (1) patient genomic information sufficient to practice the invention, to wit: to train and to exercise the neural network, **was** available on 07/06/00, **and**, to the extent that the Examiner or any finder of fact should refute this my assertion, (2) this data might alternatively readily be obtained as of 07/06/00 by a practitioner of the genomic arts having but such routine skills as then existed, and without undue, and, indeed, with little or even **no**, experimentation.

8. I have been advised that, in the required critical analysis of this my AFFIDAVIT, my skill level and/or qualifications will be analyzed as regards whether I should be found to be a routineer in the art; with the possibility that, should my skill level be found to be **higher** than that required by the routineer for a particular application, then the Examiner might challenge this my AFFIDAVIT on the grounds that it is **not** made by a routineer in the art, and therefore would not be probative as to the amount of experimentation required by a routineer in the art to implement the invention, being that I personally might be held to have a skill level or qualifications above that of the routineer in the art such as would permit me to require less experimentation to implement the claimed invention than that for the routineer.

9. To any such hypothetical finding as is hypothesized in the preceding section 8., I would argue that such hypothetical reasoning would be fallacious in that:

(1) I know what constitutes a routineer in the art of genomic data collection and compilation, and was a collector of genomic data myself in the period before 07/06/00, and I do swear and affirm in this AFFIDAVIT **from a perspective** of a less-experienced person (even though I earnestly do **not** believe this transposition to be necessary, see (4) below);

(2) this my AFFIDAVIT is directed to analyzing the adequacy of enablement **in consideration of a routineer in the art to which the invention pertains**, which abilities of a routineer I well understand <u>even if</u> I myself should somehow now be held to exceed that level;

(3) I do not agree that I could not and do not **still** constitute a routineer in the art to which the invention pertains -- albeit a routineer of a high, Ph.D., level **which I find useful, but NOT necessary in investigations in these areas, which are quite normally and routinely done by persons having graduate degrees** -- being that I do not consider myself above the work of gathering genomic data, and even if my skills were deemed not best used in actually gathering data, I might well supervise a team that did so because that is the very nature of my investigations where if one wants to analyze genomic data then one had better be prepared to compile genomic data if necessary, which I routinely do; and

(4) the whole issue of my being, or not being, a routineer is substantially irrelevant, anyhow, being that, as explained below, (i) **real routineers** were **already** gathering genomic data prior to 07/06/00, in a manner not yet recognized nor credited by the Examiner, and (ii) this data was available through routine, even if not avowedly public, sources, so that I am now simply using my expertise and knowledge **merely to report this history**, and not so as to say that I and my personal capabilities **would** necessarily be required and/or desired to accumulate such genomic data as the claimed invention requires (**although** I certainly could accumulate such data!).

10. I have been advised that I am not being asked to render opinion evidence directed to the ultimate legal question of enablement, but rather **factual evidence** directed to the amount of time and effort and level of knowledge required for the practice of the invention from the disclosure alone, which evidence serves to rebut the Examiner's "prima facie case of nonenablement", if it can be called that, under Hirschfield v. Banner, Commissioner of Patents and Trademarks , 200 USPQ 276, 281 (D.D.C. 1978).

11. To this requirement 10., I am in agreement, and I will endeavor to make a clear and cogent showing that the Application is enabling based solely on facts.

12. I have been informed that merely citing in this my AFFIDAVIT extracts from publications and journals in order to satisfy the enablement requirement is not sufficient if it is not made clear that a person skilled in the art would know which, or what parts, of the cited references could be used to construct the claimed invention or how they could be interconnected to act in combination to produce the required results (per *In re Forman*).

13. To the issue of paragraph 12., I say: The articles I now cite are prominent, their teachings clear and obvious, and any practitioner in the genomic data arts would have no problem in recognizing applicability of **both** (i) genomic data **already gathered (!!)**, and (ii) standard clinical methods of so gathering genomic data, to the claimed method of Applicants' invention.

14. In overview of my following response to the criticisms presented by the patent office, I want to emphasize in following sections 15.-16. of this AFFIDAVIT a distinction between 1.

knowledge or *information* available to a practitioner who could take advantage of the proposed technologies; and 2. the *enabling resources* available to such a practitioner.

15. By practitioner I mean a typical physician, researcher, pharmacist, or clinician (e.g., nurse, diagnostician, etc.) who might be interested in relating genetic variation to drug responsiveness with the hope of optimizing both the dosages of the drug needed for a particular patient as well as the actual drug used to treat that patient.

16. I will present arguments to the effect that not only was relevant information about genes and drug responsiveness available to practitioners that could motivate the use of the technologies proposed in the patent, but also the resources to implement the proposed technologies were available or within reach of the typical practitioner at moderate expense.

17. I now discuss Pharmacokinetics vs. Pharmacodynamics in following sections 18.-37. of this AFFIDAVIT.

18. It is well known that the mechanisms dictating the efficacious administration of drugs to treat disease have to do with 1. how much of the drug reaches its target; and 2. how the drug actually interacts with its target.

19. The amount of drug to reach its target is dictated by the drug's absorption, distribution, metabolism, and excretion rates. The study of factors that influence these parameters is termed 'pharmacokinetics.'

20. The way in which a drug interacts with its target in the human body (e.g., a specific gene, a protein, a protein complex, a circulating factor, etc.) is dictated by the structural and functional properties of the drug and its target.

21. Study of the factors that influence these parameters is termed 'pharmacodynamics.'

22. This distinction is accepted by most practitioners; see, e.g., Weber, W. W. (1997). Pharmacogenetics. New York: Oxford University Press.

23. It has been well-known that although there are many genes that influence the pharmacokinetic properties of individual drugs, there is a family of ~30 genes known as the cytochrome P450 (CYP450) gene family, characterized in 1982 (see, e.g., Gotor and Fujii-Kuriyama(1989). Evolution, structure, and gene regulation of cytochrome P450. In Basis and Mechanism of Regulation of Cytochrome P450. Ruckpaul K, Rein H (eds.). New York: Taylor and Francis, pps. 196-242.), which is known to metabolize - or be involved in the metabolism - of most endogenous compounds that the human body could be subjected to, such as food and drugs.

24. It is well known that there is a great deal of variation in CYP450 genes (see. e.g., Weber 1997, op cit.); i.e., individuals can carry different forms of the gene by having, e.g., inherited, or developed *de novo*, a mutation at a particular site in a CYP450 gene.

25. The differences among individuals that result from this genetic variation can, and are known to, influence the function of CYP450 genes (see, e.g., Weber 1997, op cit.).

26. Since this family of genes is known to influence drug metabolism, and there are known to be variations in the genes in this family that influence metabolism of endogenous compounds, variation in these genes are likely to (and have been documented to) influence the amount of drug required to elicit a particular effect in different individuals.

27. Ultimately, if a practitioner did not know *a priori* which, e.g., CYP450 genes were involved in the metabolism of a particular drug, and further, which genetic variations in CYP450 genes influenced variation in drug metabolism (which is often the case), he or she could 'genotype' a number of individuals (i.e., assess which variant at a site in a gene individuals possess) who have been or are being treated with a particular drug who have also been administered different doses based on efficacy of the drug (a routine practice by physicians and clinicians), and then use algorithms like those taught in the patent application to determine which genetic variants influence dose effects among the individuals studied.

28. The assessment of genes involved in the pharmacodynamic aspect of drug efficacy entails knowledge of genes associated with the target of the drug.

29. Since targets are numerous, there is in general no family of genes (like CYP450) that one could assume are more or less ubiquitous for drug action.

30. However, practitioners already know, or could easily familiarize themselves with, the ultimate targets of drugs by perusing the literature on the subject.

31. Once a set of genes have been identified because of their role, or possible role, in pharmacodynamic aspects of the drug, these genes can be scrutinized for variation using standard molecular biology techniques (see, e.g., Jaeckel S, Epplen JT, Kauth M, Miterski B, Tschentscher F, Epplen C (1998). Polymerase chain reaction-single strand conformation polymorphism or how to detect reliably and efficiently each sequence variation in many samples and many genes. Electrophoresis. 19:3055-61.) or publicly-accessible databases harboring information of variations in genes can be queried to find relevant genetic variations (see Gu Z, Hillier L, Kwok PY (1998). Single nucleotide polymorphism hunting in cyberspace. Human Mutation. 12:221-225.); see also the

discussion of "Resources" commencing at section 38 of the AFFIDAVIT, below.

32. If variations in the genes are found, then individuals who have been prescribed relevant drugs can be genotyped in an appropriate way (see, e.g., Ross P, Hall L, Smirnov I, Haff (1998). High level multiplex genotyping by MALDI-TOF mass spectrometry. Nature Biotechnology 16:1347-51.) and association studies can be pursued using algorithms like the one taught in the patent application to find genetic variations that influence drug efficacy.

33. The ultimate number of genes influencing complete drug responsiveness and drug dosage effects is likely to be quite large and involve genes in both pharmacokinetic and pharmacodynamic activity (e.g., if the target gene in an individual is defective, then no matter how quickly or slowly that individual may metabolize the drug due to his or her possessing relevant drug-metabolizing gene variants, the drug will not prove to be efficacious).

34. Despite this fact, knowledge of relevant genes and genetic variants for a particular drug's action, as well as resources to identify the subset of genes showing relevant variation, has been accessible to practitioners for the last 5-10 years.

35. In addition, many, many successes have been documented that relate *at least one* of the relevant gene variants to drug responsiveness (see, e.g., Weber 1997, op cit.) which anticipates hope that the others will be identified as well.

36. Of course, there is no guarantee that the genes and genetic variants (or the subjects) chosen for a study will produce positive results, but that is always a possibility in science.

37. What is important to emphasize however, is that available technologies and knowledge has worked to minimize negative outcomes to the degree possible and hence motivate practitioners to conduct relevant pharmacogenetic studies.

38. I now discuss Resources in following sections 39.-46. of this AFFIDAVIT.

39. It will be assumed that Human subjects that have been prescribed or administered drugs of relevance will be available to most practitioners; i.e., it is simply a routine medical practice to catalog drugs and dosages of drugs administered to people attending a clinic for treatment.

40. Resources for genetic studies have been at the disposal of practitioners for decades.

41. With the motivation for the Human Genome Project essentially focusing on clinical practice, and being voiced as such (see,

e.g., Collins FS. (1999). The human genome project and the future of medicine. Annals of the New York Academy of Sciences. 30:42-55), the reception of this message by the scientific community led to a number of developments which would enable pharmacogenetics research in various ways.

42. For example, the notion of identifying genetic variants to facilitate the identification of individual variation in disease susceptibility, drug response, and response to environmental stimuli of all sorts, was proposed as an item of emphasis by leaders at the National Institutes of Health and the Human Genome Project (see, Collins FS, Patrinos A, Jordan E, Chakravarti A, Gesteland R, Walters L (1998). New goals for the U.S. Human Genome Project: 1998-2003. Science. 282: 682-689.) and this led to research grant support for various studies and practices.

43. This emphasis led to the creation of databases (see, e.g., Collins FS, Brooks LD, Chakravarti A (1998). A DNA polymorphism discovery resource for research on human genetic variation. Genome Research. 8:1229-31; Gu et al. 1998, op cit.; and Wang et al. 1998, op cit.) containing information about variation in human genes.

44. These databases are, and have been for years, publicly accessible such that any practitioner could query them.

45. This emphasis also led to developments in high-throughput genotyping assays (see, e.g., Jaeckel et al. 1998) which would enable practitioners to develop assays based on genes and genetic variation information they may have gathered from available sources for genotyping purposes.

46. These practitioners could then genotype individuals for which treatment data are available using standard techniques, and then try to associate subsets of the genetic variations with responsiveness with algorithms like those proposed in the patent application.

47. I have caused to be attached the references that I have cited in this AFFIDAVIT on a separate sheet for the convenience of the Patent Examiner.

48. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent(s) issued thereon.

3/17/03
date

Nicholas J. Schork
signature of Nicholas Schork

References

Collins FS, Brooks LD, Chakravarti A (1998). A DNA polymorphism discovery resource for research on human genetic variation. Genome Research. 8:1229-31.

Collins FS, Patrinos A, Jordan E, Chakravarti A, Gesteland R, Walters L (1998). New goals for the U.S. Human Genome Project: 1998-2003. Science. 282: 682-689.

Collins FS. (1999). The human genome project and the future of medicine. Annals of the New York Academy of Sciences. 30:42-55;

Gotor R, Fujii-Kuriyama (1989).Evolution, structure, and gene regulation of cytochrome P450. In Basis and Mechanism of Regulation of Cytochrome P450. Ruckpaul K, Rein H (eds.). New York: Taylor and Francis, pps. 196-242.

Gu Z, Hillier L, Kwok PY (1998). Single nucleotide polymorphism hunting in cyberspace. Human Mutation. 12:221-225.

Jaeckel S, Epplen JT, Kauth M, Miterski B, Tschentscher F, Epplen C (1998). Polymerase chain reaction-single strand conformation polymorphism or how to detect reliably and efficiently each sequence variation in many samples and many genes. Electrophoresis. 19:3055-61.

Ross P, Hall L, Smirnov I, Haff (1998). High level multiplex genotyping by MALDI-TOF m spectrometry. Nature Biotechnology 16:1347-51.

Wang DG, Fan JB, Siao CJ, Berno A, Young P, Sapolsky R, Ghandour G, Perk E, Spencer J, Kruglyak L, Stein L, Hsie L, Topaloglou T, Hubbell E, Robir Morris MS, Shen N, Kilburn D, Rioux J, Nusbaum C, Rozen S, Hudso Large-scale identification, mapping, and genotyping of single-nucl human genome. Science. 1998 280:1077-82.

Weber, W. W. (1997). Pharmacogenetics. New York